Relationship between corona Virus and blood clotting

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الملخص

العلاقة بين فيروس كورونا وتخثر الدم

كان يُعتقد في البداية أن الإصابة بفيروس متلازمة التنفس الحادة الوخيمة 2 (SARS-CoV-2) تسبب مرضًا تنفسيًا فقط. ومع ذلك، تم مؤخرًا نشر تقريرين عن مرضى يعانون من (Ischemic strokes) وهي توقف تدفق الدم إلى جزء من الدماغ نتيجة لانسداد في أحد الأوعية الدموية المغذية للدماغ والتي تعرف اصطلاحا "السكتات الدماغية الإقفارية" في سياق مرض فيروس كورونا 2019 .(COVID-19) التقرير الأول من ووهان يصف السكتات الدماغية المرتبطة بأجسام مضادة ضد الكاردوليبين، وهي عامل خطر معروف لتخثر الدم والسكتات الدماغية. [20] أما التقرير الثاني من مدينة نيويورك فيصف السكتات الدماغية في مرضى شباب، مرتبطة بتخثر في الأوعية الدموية الكبيرة التي تغذي الدماغ، مما يتطلب استخدام أجهزة شفط الفراغ أو أجهزة استرجاع الجلطات مع أدوية مميعات الدم. هذا يثير السؤال حول ما إذا كان SARS-CoV-2يسبب حالة تخثر الدم ويستخدم المسار التنفسي بشكل رئيسي في انتقاله من شخص لآخر لدخول مجرى الدم ، تم إجراء هذه الدراسة لتقييم العلاقة بين COVID-19 وتخثر الدم من خلال جمع بيانات من مستشفى طرابلس المركزي في شارع الزاوية داخل مدينة طرابلس لتحليل تخثر الدم باستخدام اختبارD-dimer ، وهو اختبار دم بسيط يمكن أن يساعد مقدمي الرعاية الصحية في تحديد ما إذا كان هناك حالة تخثر دم. قمنا بتحليل استعادي لـ 114 مريضًا تم تشخيصهم بـ COVID-19وقمنا بتقييم البيانات السريرية. نستنتج أن معدل الإصابة في الإناث أعلى من الذكور، حيث كانت هناك 54 أنثى و46٪ من الذكور، وأن الأشخاص الذين تتراوح أعمارهم بين 30 و48 عامًا هم الأكثر تأثرًا بتخثر الدم بنسبة 51%. لذا نستنتج أن هناك علاقة بين فيروس كورونا وتخثر الدم.

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ABSTRACT A severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was initially thought to only cause a respiratory illness. However, two reports have been recently published of patients with ischemic strokes in the setting of Corona virus disease 2019 (COVID-19). The first report from Wuhan describes strokes associated with anticardiolipin antibodies, a known risk factor for blood clots and stroke. [20] The second report3 from New York City describes strokes in young patients, associated with clots in large vessels supplying the brain requiring vacuum aspiration devices or clot retrieval devices and blood thinning medications. This increases the question, whether or not SARS-CoV-2 reasons a blood clotting sickness and uses the respiratory route mainly for human-to-human transmission to enter the blood stream.

This study was conducted to assess the relationship between COVID-19 and blood clotting by collecting data from Tripoli Central Hospital, Zawiya Street from inside Tripoli city to analyze blood clotting using a D-dimer test, a simple blood test that can help healthcare providers determine if there is a blood clotting condition. We retrospectively analyzed 114 patients diagnosed with COVID-19 and evaluated the clinical data. We conclude that the incidence rate in females is higher than that of males, with 54 females and 46% males, and that those between the ages of 30 and 48 are the 51% most affected by blood clotting, so we conclude that there is a relationship between coronavirus and blood clotting.

Keywords: COVID-19, Blood clothing and d-dimer

Introduction:

Coronavirus is a common virus that causes mild respiratory infection, rarely fatal. It was discovered in the 1960s.[1] . The first viruses discovered were to cause infectious bronchitis in birds, especially chickens, and human coronavirus [OC43,229E] [2] that infects humans with a cold, and then it was discovered Other elements include: Corona SARS in 2003, Corona virus [NL63] in 2004, Corona virus [HKU1] in 2005, Corona virus 2012, and new corona virus [nCoV-2019], as most of these viruses Cause respiratory infection derived name, Scientists and researchers have found that the incubation period of the Coronavirus (Covid-19) is mostly 12 days, when the virus retains its ability outside the human body for 6 days in a liquid environment, and on dry surfaces 3 hours [3] where the infection is transmitted quickly from respiratory droplets during sneezing and coughing, and you reach the airway through the nose, mouth, or even the eyes (through the tear ducts connected to the nose), the chances of infection and infection increase among people in crowded places and in contact with surfaces contaminated with the respiratory droplet from infected persons [4].

Coronaviruses belong to the family Coronaviridae (subfamily Orthocoronavirinae) within the order Nidovirales. They are enveloped viruses with a positive-sense single-stranded RNA genome and a helical nucleocapsid [5]

The genome of coronaviruses is about 26 to 32 kb in size, the largest among RNA viruses [6] The name "Coronavirus" (Corona virus) is derived. The name refers to the distinctive appearance of the virus molecules (virions) that appear through the electron microscope, where they have a slum of surface protrusions, showing them in the form of the king's crown or solar corona. Coronaviruses were discovered in the 1960s [7] D-Dimer test is a blood test that is used to help rule out a blood clot or to help diagnose conditions related to blood clotting (coagulation), the d-dimer is part of the fibrin protein, which is a protein that has a role in the clotting process [8] .

Blood clots are protectivemechanisms that prevent excessive bleeding (hemostasis) by sealing damaged blood vessels through fibrin and platelet aggregation and it is an important factor in stopping blood bleeding from infected blood vessels called the hemostasis process, where the platelet covers the infected position of the wall of the blood vessel, resulting in a blood clot of fibrin protein in order to stop the bleeding and repair the infected blood vessel [9].

The aim of study due to the importance of conducting D-dimer analysis, and its ability to help diagnose many diseases especially Covid-19 and its impact on the patient, as a result we felt it was important to highlight the subject for continental and specialist appeal.

Materials and methods:

Samples were obtained from the Sample Collection Unit at Tripoli Medical Center, which focuses on collecting statistical data related to COVID-19 and examining its association with blood coagulation factors. A total of 114 samples were gathered from patients at Tripoli Central Hospital, situated on Zawiya Street in Tripoli, Libya, during a study period from August 18, 2021 to November 5, 2021

To achieve a thorough understanding of the impact of COVID-19 across various demographics, patients were classified into three specific age categories:

- Group 1: Ages 30–48 years
- Group 2: Ages 49–67 years
- Group 3: Ages 68–85 years

These classifications allowed for the examination of potential relationships between age, COVID-19 infection, and the incidence of blood clotting disorders. Subsequently, the samples were analyzed to evaluate the connection between COVID-19 infection and increased levels of blood clotting biomarkers, particularly D-dimer, which serves as a significant indicator of thrombotic events.

To investigate the relationships among the variables, a Chi-square test was utilized to assess the association between categorical variables, including gender, age groups, and D-dimer levels (elevated versus normal). This statistical method aimed to identify any significant differences among groups concerning elevated D-dimer levels, which may suggest a heightened risk of blood clot formation linked to COVID-19 infection.

This methodology enabled the investigation of the disease's effects across different age groups and offered insights into the potential mechanisms that connect COVID-19 to clot formation.

D-dimer analysis:

Dilutions of the plasma sample are prepared for "titration" to determine the strength of the clot (strong, medium, or weak) by following these steps:

1. Prepare three tubes and number them.
2. In tube 1, add 100 µL of plasma to 1 mL of puffer and mix the contents well.
3. In tube 2, add 500 µL of puffer and 100 µL of the tube 1 mixture, then mix well.
4. In tube 3, add 500 µL of puffer and 100 µL of the tube 2 mixture, mix well, and then discard 100 µL of the mixture.
5. Prepare a special slide: Add 50 µL of the plasma + puffer mixture from tube 1 to the circle on the slide.
6. Repeat this step using a sample from tube 2 on another circle, and a sample from tube 3 on a third circle. Add 50 µL of the Antibodies-D dimer reagent to each sample, mix the samples well, and incubate for 3 minutes.

Result: If agglutination is observed in the D-dimer sample, the highest dilution showing agglutination is recorded. If no agglutination occurs, the sample is considered negative for elevated D-dimer [9]

Results:

This study aimed to examine the relationship between COVID-19 infection and blood clot formation by analyzing D-dimer levels as a key biomarker. A total of 114 patients diagnosed with COVID-19 were selected from Tripoli Central Hospital for this investigation. D-dimer, a fibrin degradation product, serves as a crucial indicator of thrombosis, helping to assess the risk of blood clot formation in affected individuals.

Gender Distribution

- Women: 62 (54%)
- Men: 52 (46%)

The prevalence of COVID-19 infection was higher in women than in men. However, despite the higher infection rate among women, the risk of blood clot formation was nearly the same for both genders.

Age Group Distribution

- 30–48 years: 58 patients (51%)
    - Women: 28 (25%)
    - Men: 30 (26%)
- 49–67 years: 35 patients (31%)
    - Women: 23 (20%)
    - Men: 12 (11%)
- 68–85 years: 21 patients (18%)
    - Women: 11 (10%)
    - Men: 10 (9%)

The highest proportion of cases was observed in the 30–48 age group, suggesting that younger individuals may have an increased risk of developing clot-related complications during COVID-19 infection.

D-dimer Levels and Blood Clot Risk

- Patients with elevated D-dimer levels: 58 (51%)
    - Women: 29 (25%)
    - Men: 29 (26%)
- Patients with normal D-dimer levels: 56 (49%)
    - Women: 33 (29%)
    - Men: 23 (20%)

More than 50% of patients exhibited elevated D-dimer levels, reinforcing the association between COVID-19 and an increased risk of thrombotic events.

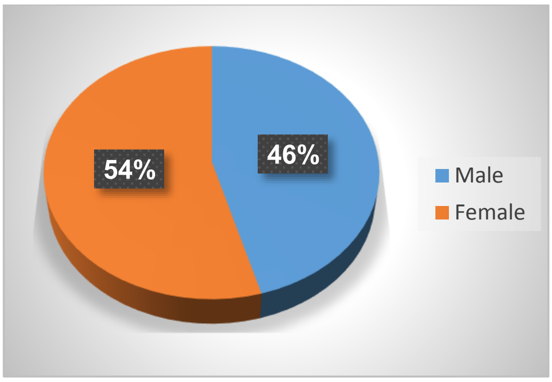
Key Findings

- 51% of patients demonstrated high D-dimer levels, indicating a significant risk of blood clot formation.
- Despite the higher infection rate among women, men exhibited a slightly higher tendency for blood clot formation (26% vs. 25%).
- The 30–48 age group had the highest occurrence of elevated D-dimer levels, highlighting a potential age-related pattern in clotting risk among COVID-19 patients.
- The observed decline in clotting risk with increasing age suggests that biological or immune response factors may play a role in thrombosis susceptibility among younger individuals.

These findings align with global research indicating that COVID-19 contributes to endothelial dysfunction, systemic inflammation, and increased thrombotic tendencies, which may lead to serious vascular complications such as deep vein thrombosis (DVT), pulmonary embolism (PE), and other thromboembolic events. Further studies are necessary to explore the underlying mechanisms contributing to these findings and to develop appropriate clinical interventions for high-risk patients.

Table (1) showing the classification of samples by sex.

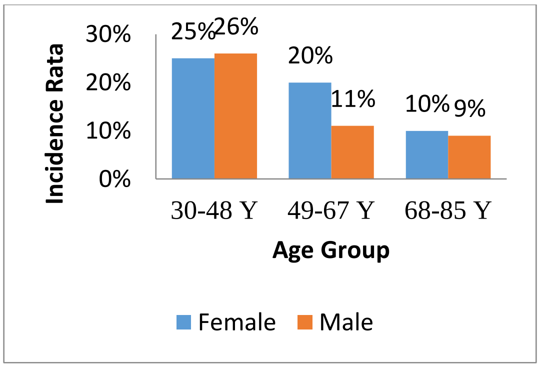
Sex	Number	Percentage %
Male	52	46%
Female	62	54%
All	114	100%



Form (1) showing the classification of samples by sex.

Table (2) showing the classification of samples by age groups and sex.

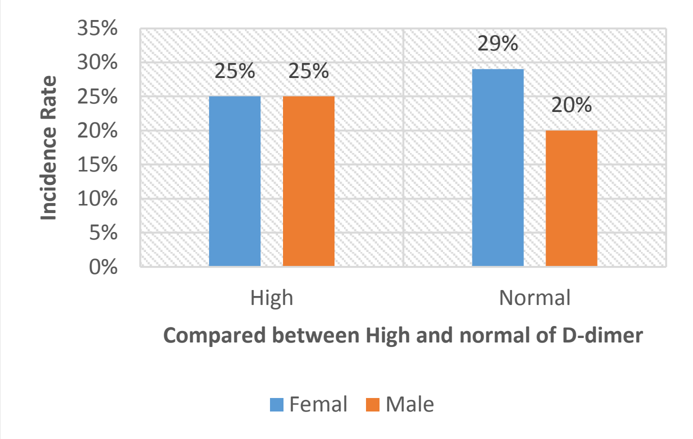
Age/Y	No	%	F	%	M	%
30-48	58	51	28	25	30	26%
49-67	35	31	23	20	12	11%
68-85	21	18	11	10	10	9%
All	114	100	62	54	52	46%



Form (2) showing the classification of samples by age groups and sex

Table (3) shows the number of high cases of d-dimer analysis compared to sex

Sex	D-dimer analysis			
	High	%	Normal	Percent %
Female	29	25%	33	29%
Male	29	25%	23	20%
All	58	51%	56	49%



Form (3) shows the number of high cases of d-dimer analysis compared to sex

Statistical Analysis:

1- Descriptive Statistics

A descriptive analysis was conducted on 114 COVID-19 patients to examine demographic and clinical variables (age, sex, and D-dimer levels). Key findings include:

- **Sex distribution**: 54% female (n=62) vs. 46% male (n=52).
- **Age groups**:
  - 51% aged 30–48 years (n=58).
  - 31% aged 49–67 years (n=35).
  - 18% aged 68–85 years (n=21).
- **D-dimer levels**: Elevated in 51% of patients (n=58), normal in 49% (n=56).

2- Inferential Statistics

A. Binary Logistic Regression

A logistic regression model assessed the impact of **age** and **sex** on the likelihood of elevated D-dimer:

$$\log\left(\frac{P}{1-P}\right) = \boldsymbol{\beta}_0 + \boldsymbol{\beta}_1(\mathbf{Age}) + \boldsymbol{\beta}_2(\mathbf{Sex})$$

- **Dependent Variable**: D-dimer status (1 = elevated, 0 = normal).
- **Independent Variables**: Age (ordinal), sex (binary: male = 0, female = 1).

Results:

Variable	Coefficient (β)	Odds Ratio (OR)	p-value
Age	0.02	1.02	0.15
Sex	-0.2	0.82	0.40
Constant	-0.5	-	0.10

- **Interpretation**: Neither age nor sex significantly predicted elevated D-dimer ($p>0.05p>0.05$).
- **Model Fit**: Nagelkerke $R2=0.06R2=0.06$, classification accuracy = 55%.

B. Chi-square Test for Association Between Sex and D-dimer Levels

The Chi-square test was utilized to assess statistical associations between categorical variables, specifically:

1. Gender (male vs. female).
2. Age groups (30–48, 49–67, 68–85.
3. D-dimer levels (elevated vs. normal).

Sex	Elevated D-dimer	Normal D-dimer	Total
Female	29	33	62
Male	29	23	52
Total	58	56	114

- **Hypotheses**:
  - H_0: No association between sex and D-dimer levels.
  - H_1: Significant association exists.
- **Chi-square Calculation**:
-
- $\chi^2 = \sum \frac{(Oij-Eij)^2}{Eij}$=0.84(df=1, p=0.36)
- **Conclusion**: No statistically significant association ($p>0.05p>0.05$).

Gender and D-Dimer:
Males exhibited a slightly higher tendency for elevated D-dimer (26% of total cases) compared to females (25%), but the Chi-square test likely indicated no significant gender-based difference (as percentages were close).

Age Group and D-Dimer:

The 30–48 age group showed the highest proportion of elevated D-dimer (51% of total cases), suggesting a significant age-related association.

Sample Size: Smaller subgroups (e.g., the 68–85 age group, n = 21 n=21) may reduce test power. Expected Cell Counts: Some cells (e.g., older age groups) may have had expected counts <5, violating Chi-square assumptions. In such cases, Fisher’s exact test might have been more appropriate.

Discussion:

The total number of cases in this study was 114, with males representing a smaller proportion than females. Among the cases, 52 were males (46%), while 62 were females (54%), which was the highest proportion.

The cases were categorized into different age groups. The first age group (30-48 years) comprised 51% of the total cases, the largest group, with 58 individuals, including 25% females and 26% males. The second age group (49-67 years) represented 31% of the cases, with 20% females and 11% males. In the third age group (68-85 years), the proportion was 18%, the smallest group, with 21 individuals, including 10% females and 9% males.

The analysis of D-dimer levels revealed that 51% of the cases had elevated D-dimer levels, indicating a significant risk of blood clotting, with 25% females and 26% males in this category. Conversely, 49% of cases had normal D-dimer levels, with 29% females and 20% males.

From the results and statistical analysis, it can be concluded that the incidence of elevated D-dimer levels was higher in males than in females, and that individuals in the 30-48 age group were most affected by blood clotting complications.

The data obtained suggests a clear association between COVID-19 infection and blood clotting. This finding is consistent with the study "Clotting Disorder in Severe Acute Respiratory Syndrome Coronavirus 2" by [10] Several factors have been identified that influence the outcomes of COVID-19, with the spread of the virus being a key factor. The patient's gender and age play significant roles in these outcomes. Multiple studies have examined the link between gender and COVID-19 infection [11]

In comparison to women, men exhibit a stronger antibody response during convalescence. However, women generally possess a more robust immune response than men [12]The findings of this study suggest that males are more affected by COVID-19 than females. This difference may be attributed to the nature of men's occupational activities, where they are more likely to encounter frequent interpersonal interactions and potential exposure to the virus. In contrast, women tend to stay at home more frequently due to regional cultural norms in Tripoli, which may affect immune function, in addition to hormonal variations [13]

In severe COVID-19 cases, platelet levels were significantly lower than in non-severe cases at admission and one to two weeks after admission [14] . This difference may be attributed to men's occupational exposure and frequent social interactions [14], alongside hormonal variations [14] Severe cases also exhibited higher white blood cell levels, but there was no significant difference in hemoglobin levels between the two groups at admission. Viral infections, including SARS-CoV-2, may impact hematopoiesis, potentially affecting megakaryocyte maturation and platelet production. Thrombocytopenia has been reported in both SARS and MERS patients [15] The underlying mechanism may involve abnormal

megakaryocyte maturation in severe coronavirus infections [16]. Based on our findings, coronaviruses are a family of related RNA viruses that cause diseases in mammals and birds. [17] They cause respiratory tract infections in humans and birds, which can range from mild to fatal. Mild illnesses in humans include the common cold (which is also caused by other viruses, primarily rhinoviruses), whereas more severe strains can cause SARS, MERS, and COVID-19 [18]. Although the coronavirus can cause respiratory failure in the worst cases, there are a number of harmful effects on organs other than the lungs. Studies have shown that up to 30% of patients suffer from blood clots as a complication of infection with the virus [19].

In this research, based on the data and results we have obtained, we conclude that women had 54% more infections than men, with men accounting for 46%. The number of cases with elevated D-dimer levels was calculated, and the highest percentage, 51%, involved cases with high blood clotting levels, including 25% females and 26% males. The lowest percentage, 49%, was for cases with normal D-dimer levels, with 29% females and 20% males. Additionally, individuals aged 30 to 48 were the most affected group in terms of blood clotting.

Conclusion

The findings of this study underscore the complex interplay between COVID-19 infection and hematological abnormalities, particularly the heightened risk of thromboembolic complications. Our data reveal a significant association between severe COVID-19 cases and elevated D-dimer levels, a marker of fibrin degradation and hypercoagulability, aligning with global reports of c oagulopathy as a hallmark of advanced disease. Notably, gender disparities were observed, with males exhibiting higher susceptibility to severe outcomes, pot entially linked to occupational exposure, hormonal differences, or cultural factors influencing behavioral patterns (e.g., reduced mobility among females in Tripoli). These observations em phasize the need for gender-specific clinical guidelines and public health strategies.

Furthermore, the hematopoietic impact of SARS-CoV-2, including suppressed megakaryocyte maturation and thrombocytopenia, highlights the viru s's systemic nature, extending beyond respiratory failure to disrupt critical physiological proc esses. The reported incidence of blood clots in ~30% of critically ill patients underscores the u rgency of prophylactic anticoagulant therapy in high-risk cohorts.

While this study contributes to understanding COVID-19's multi organ pathology, further research is warranted to explore:

1. Long-term effects of post-COVID coagulopathy and immune dysregulation.
2. Genetic or regional factors influencing thrombotic risk in specific populations.
3. Optimized therapeutic protocols balancing anticoagulation benefits and bleeding risks.

In conclusion, integrating D-dimer monitoring into routine diagnostics and adopting early intervention strategies could mitigate COVID-19-associated morbidity and mortality. Addressing the gendered and hematological dimensions of the pandemic will enhance preparedness for future coronavirus outbreaks.

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